Comparative evaluation of three clinical decision support systems: prospective screening for medication errors in 100 medical inpatients

Fritz, Daniela ; Ceschi, Alessandro ; Curkovic, Ivanka ; Huber, Martin ; Egbring, Marco ; Kullak-Ublick, Gerd A ; Russmann, Stefan

Abstract: PURPOSE: Clinical decision support systems (CDSS) are promoted as powerful screening tools to improve pharmacotherapy. The aim of our study was to evaluate the potential contribution of CDSS to patient management in clinical practice. METHODS: We prospectively analyzed the pharmacotherapy of 100 medical inpatients through the parallel use of three CDSS, namely, Pharmavista, DrugReax, and TheraOpt. After expert discussion that also considered all patient-specific clinical information, we selected apparently relevant alerts, issued suitable recommendations to physicians, and recorded subsequent prescription changes. RESULTS: For 100 patients with a median of eight concomitant drugs, Pharmavista, DrugReax, and TheraOpt generated a total of 53, 362, and 328 interaction alerts, respectively. Among those we identified and forwarded 33 clinically relevant alerts to the attending physician, resulting in 19 prescription changes. Four adverse drug events were associated with interactions. The proportion of clinically relevant alerts among all alerts (positive predictive value) was 5.7, 8.0, and 7.6%, and the sensitivity to detect all 33 relevant alerts was 9.1, 87.9, and 75.8% for Pharmavista, DrugReax and TheraOpt, respectively. TheraOpt recommended 31 dose adjustments, of which we considered 11 to be relevant; three of these were followed by dose reductions. CONCLUSIONS: CDSS are valuable screening tools for medication errors, but only a small fraction of their alerts appear relevant in individual patients. In order to avoid overalerting CDSS should use patient-specific information and management-oriented classifications. Comprehensive information should be displayed on-demand, whereas a limited number of computer-triggered alerts that have management implications in the majority of affected patients should be based on locally customized and supported algorithms.

DOI: https://doi.org/10.1007/s00228-012-1241-6

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Comparative Evaluation of Three Clinical Decision Support Systems: Prospective Screening for Medication Errors in 100 Medical Inpatients

Daniela Fritz[1], Alessandro Ceschi[1,2], Ivanka Curkovic[1], Martin Huber[1], Marco Egbring[1], Gerd A. Kullak-Ublick[1,3], Stefan Russmann[1,3]

[1] Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland

[2] Swiss Toxicological Information Center, Zurich, Switzerland

[3] Zurich Center for Integrative Human Physiology (ZIHP), Zurich, Switzerland

Word count: 3,324

Correspondence:
Stefan Russmann, MD
Department of Clinical Pharmacology and Toxicology, University Hospital Zurich
Rämistrasse 100, 8091 Zurich, Switzerland
phone: +41 44 255 20 67
fax: +41 44 255 44 11
e-mail: stefan.russmann@usz.ch

ABSTRACT

Purpose Clinical decision support systems (CDSS) are promoted as powerful tools to improve pharmacotherapy. We aimed to evaluate the potential contribution of CDSS to patient management in clinical practice.

Methods We prospectively analyzed the pharmacotherapy of 100 medical inpatients through the parallel use of the CDSS Pharmavista, DrugReax and TheraOpt. After expert discussion that also considered all patient-specific clinical information we selected apparently relevant alerts, issued according recommendations to physicians and recorded subsequent prescription changes.

Results For 100 patients with a median of eight concomitant drugs Pharmavista, DrugReax and TheraOpt generated a total of 53, 362 and 328 interaction alerts, respectively. Among those we identified and forwarded 33 clinically relevant alerts that were followed by 19 according prescription changes. Four adverse drug events were associated with interactions. The proportion of clinically relevant alerts among all alerts (positive predictive value) was 5.7, 8.0 and 7.6%, and the sensitivity to detect all 33 relevant alerts 9.1, 87.9 and 75.8% for Pharmavista, DrugReax and TheraOpt, respectively. TheraOpt recommended 31 dose adjustments, of which we considered 11 as relevant, and three were followed by dose reductions.

Conclusions CDSS are valuable screening tools for medication errors, but only a small fraction of their alerts appear relevant in individual patients. In order to avoid overalerting CDSS should use patient-specific information and management-oriented classifications. Comprehensive information should be displayed on-demand, whereas a limited number of computer-triggered alerts that have management implications in the majority of affected patients should be based on locally customized and supported algorithms.

Keywords: Clinical decision support software, dose adjustment, drug interactions

INTRODUCTION

Adverse drug events (ADE) are an important cause of morbidity, mortality and increased healthcare costs and therefore a challenging problem for clinical patient care [1-7]. Drug interactions and dosing errors leading to ADE are of special interest because they represent preventable medication errors that are suitable targets for highly efficient automated interventions through computerized physician order entry (CPOE) with clinical decision support systems (CDSS). The efficacy of CDSS to affect physicians' behavior in clinical practice and thereby to reduce medication errors and improve monitoring of pharmacotherapy has been well established, whereas their efficacy to reduce ADE and costs is less well documented and needs further investigation [8-15]. Furthermore, only few studies compared the performance of different CDSS, and even those were usually not conducted under real-life conditions. Classification and grading of medication errors is a complex and challenging task, and previous studies reported major disagreements in the assessment of drug interactions between different CDSS [16-18] and specialists [19]. Furthermore, general assessments may not well apply to specific patients where prescribing clinicians also use additional complex non-standardized clinical information for management decisions [20, 21]. Generally, it appears that most CDSS have a high sensitivity to detect drug interactions at the cost of low specificity to discriminate those interactions that are clinically relevant. In combination with insufficient consideration of patient-specific factors by CDSS this leads to indiscriminate overriding of alerts by prescribing clinicians, which jeopardizes the efficacy of CDSS to improve medication safety in clinical practice [22].

For our routine clinical pharmacology "safety ward rounds" we use several CDSS as an initial screening tool to search for drug interactions and dosing errors in hospitalized patients. However, given the limitations mentioned above, after automated screening we also access the electronic medical records of the respective patients in order to evaluate the clinical relevance of potential medication errors initially identified by CDSS. Only if we conclude that a potential medication error is clinically relevant in the patients' individual clinical context, we alert the responsible physician and discuss alternatives as appropriate. Because there is a

need for systematic evaluations of the performance of different CDSS in real-life clinical settings the current study analyzed our experience with the use of different CDSS in combination with clinical pharmacology expertise for the identification and prevention of medication errors.

METHODS

Study design

We present a prospective naturalistic analysis that evaluated the performance of CDSS used as part of our surveillance of pharmacotherapy at two general internal medicine wards of a tertiary care university hospital. Our surveillance has the aim to optimize efficacy and safety of pharmacotherapy. Because this study is a systematic analysis of our established routine clinical practice it was exempt from ethical approval. A summary of the procedures is presented in **Figure 1**. The study includes 100 consecutive patients for an evaluation of all concomitantly prescribed drugs with a focus on potential drug interactions. There were no formal exclusion criteria. A formal power analysis was not applicable in this descriptive pilot analysis, and the decision to include 100 patients was based on pragmatic and somewhat arbitrary grounds. As our surveillance is performed at certain days of the week and patients may also had been transferred from other wards, the day of analysis in relation to hospital admission varied. All concomitantly prescribed drugs were simultaneously analyzed with three different CDSS, i.e. Micromedex DRUG-REAX®, Atheso TheraOpt® (which in the meantime has been taken over by ID Berlin), and Pharmavista® [23-25]. Of note, Pharmavista did not allow the entry of more than eight concomitantly used drugs at a time, and for patients using more than eight drugs an interaction analysis could therefore not be performed with Pharmavista. Automatically generated alerts from all three CDSS were documented. Subsequently at least one junior and one senior clinical pharmacologist from our department discussed and evaluated the automatically generated alerts for their clinical

relevance in the individual clinical context of each patient. Alerts were defined as clinically relevant if we considered a change of therapy as necessary. For that purpose we also accessed the hospital's clinical information system containing all electronic drug prescriptions, medical reports and laboratory results. Subsequently we forwarded only presumably clinically relevant alerts to the treating physician, usually by personal communication during ward rounds or over the phone, plus an entry into the electronic patient record. If appropriate we also provided additional information and management recommendations including possible alternative therapies and monitoring. Thereafter we followed the electronic prescribing record for those patients until hospital discharge in order to document whether prescriptions were changed in accordance with our recommendations. Furthermore, we also specifically searched medical reports and laboratory results for signs and symptoms of ADE that may have resulted from prescriptions addressed in the alerts.

Outcomes and data analysis

Primary outcomes of the study were the comparative number of alerts generated by each CDSS, and the fractions thereof that we considered as clinically relevant and therefore forwarded to the treating physicians. In order to compare the performance of the three CDSS we calculated their sensitivity and positive predictive value (PPV) regarding the identification of clinically relevant drug interactions as follows. Sensitivity = number of interactions among all interactions evaluated as clinically relevant identified by the respective CDSS divided by all interactions evaluated as clinically relevant identified by any CDSS or during expert discussion; PPV = number of interactions identified by the respective CDSS and evaluated as clinically relevant divided by the number of interactions identified by the respective CDSS. We compared the sensitivity and PPV between different CDSS using the chi square test. Additional measures of interest included the number of actual medication changes in response to those alerts that we had forwarded to the treating physicians, as well as stratified analyses, e.g. by CDSS grading, and description of specific alerts and associated ADE. Data

management, analyses and figures were done using STATA 11.2 for MacOS X (STATA corporation, College Station, TX, USA).

RESULTS

Patient characteristics and drug use

Demographic and clinical characteristics of all 100 included patients are presented in **Table 1**. The median age was 59.3 years (range 23 - 86), and in 70 patients the pharmacotherapy was analyzed between days 2 and 9 after admission (median and mean 5 and 6.5 days, respectively). Forty-four patients had impaired renal function with a glomerular filtration rate (GFR) below 60 ml/min, 11 had liver disease with a CHILD score ≥7, 23 had undergone organ transplantation at any time in the past, and 25 patients had malignant tumors.
Table 2 presents the most commonly prescribed drugs in the study population. Overall there were 892 prescriptions in 100 patients. Based on the presented classification antibiotics ranked as the most frequently prescribed drug class accounting for 110 prescriptions (12.3%) in 50 patients, followed by heparins, proton pump inhibitors, diuretics and beta-blockers.
A histogram of the polypharmacy distribution is shown in **Figure 2**. The mean and median number of concomitant substances prescribed to each patient was 8.9 and 8, respectively.

Drug interactions

The correlation between polypharmacy and the mean number of identified interactions per patient by each CDSS is shown in **Figure 3**. As expected based on the exponential increase of possible combinations, increasing polypharmacy was also associated with a pronounced increase of identified interactions. Because Pharmavista could only analyze up to eight concomitantly prescribed drugs, there are no results from Pharmavista for patients receiving more than eight drugs. Consequently the overall number of interactions identified by Pharmavista was much lower compared to DrugReax or Theraopt (Pharmavista 53,

DrugReax 362, TheraOpt 328). As expected, for patients receiving up to eight drugs differences in the number of identified interactions were smaller (Pharmavista 53, DrugReax 75, TheraOpt 56). An overview of the identification of drug interactions by each CDSS including our subsequent expert evaluation and implementation of the resulting recommendations by the treating physicians is provided in **Table 3**. Among all interaction alerts generated by any CDSS we evaluated 33 interactions as clinically relevant in the individual clinical context of the respective patients. Of note, when a CDSS classified an alert as severe and we did not forward this alert to the treating physician, the reason for our decision was documented. For example, there were five “severe” pharmacokinetic interaction alerts with cyclosporine, but therapeutic drug monitoring indicated appropriate dose adjustment with concentrations in the therapeutic range. Other examples include the combination of several drugs that increase the risk of bleeding when there was an evidence-based indication for this combination, or the combination of several potassium sparing drugs when potassium concentrations were indeed normal and stable. The proportion of generated alerts that we considered as clinically relevant (which corresponds to the PPV) was comparable for the three CDSS, i.e. between 5.7 and 8% ($p > 0.1$ for all comparisons). The sensitivity to detect the 33 relevant interactions was 87.9% for DrugReax, 75.8% for TheraOpt, and 9.1% for Pharmavista ($p < 0.001$ for TheraOpt or DrugReax vs. Pharmavista; $p > 0.1$ for DrugReax vs. TheraOpt). Further stratification by severity classification (**Table 3**) showed a poor correlation between CDSS severity class and our evaluation of clinical significance for individual patients, and that DrugReax assigned a higher proportion of its alerts to a higher severity class than TheraOpt. A detailed description of all relevant interactions is presented in **Table 4**. Amiodarone was involved in eight interactions, antimycotics in seven, and statins and immunosuppressants in six each. Pharmacokinetic and pharmacodynamic interaction mechanisms were involved with an about equal frequency. For 19 of the 33 forwarded alerts (57.6%) we observed a subsequent prescription change that was in line with our recommendations.

Dosing

TheraOpt is also able to identify dosing errors based on recommended maximum doses for specific indications, gender, age, and renal and liver function. We used this feature for an evaluation of appropriate dosing for all prescriptions. TheraOpt recommended 31 dose adjustments, and we found one additional dosing problem related to decreased first pass of metoprolol in cirrhosis. Among those we considered 11 as justified and forwarded recommendations for prescription changes, which were followed by according changes in three cases (**Table 5**).

Adverse drug events

In four patients we detected adverse events that were possibly related to the identified interaction or dosing issues. In the first case oral ciprofloxacin was combined with oral calcium, and the patient developed cholecystitis and E. coli sepsis. Impaired absorption of ciprofloxacin may have contributed to treatment failure, leading to prolonged hospitalization in this case. In the second case a patient developed hypokalemia (2.9 mmol/l) under combined therapy with hydrochlorothiazide, torasemide and prednisone. After medication change the patient's serum potassium quickly normalized. The third patient concomitantly received itraconazole capsules and pantoprazole. Proton pump inhibitors are known to impair the bioavailability of itraconazole capsules [26], and drug monitoring indeed showed subtherapeutic itraconazole concentrations (0.2 mg/l, target level is above 1). The fourth patient had a transjugular intrahepatic portosystemic shunt (TIPS) and received 6 mg budesonide per day for autoimmune hepatitis with cirrhosis stage Child B. This patient developed a thrombosis of the TIPS. Elevated bioavailability of budesonide due to portocaval shunting in association with portal vein thrombosis has been described [27], and elevated concentrations may have contributed to TIPS thrombosis here.

DISCUSSION

This study presents a systematic analysis of our experience with three different CDSS used as screening tools for medication errors in daily clinical routine.

First, our results provide information on the occurrence of specific medication errors in the studied setting. Amiodarone, antimycotics, cholesterol lowering HMG-CoA-reductase inhibitors and immunosuppressants were most frequently involved in relevant interactions, underlining that any prescribing physician should give particular attention to their interaction profiles and routinely check for interactions when prescribing these drugs. Of interest, a previous study using a different CDSS in a different population of 84,607 psychiatric inpatients also found amiodarone to have the highest intrinsic risk of interactions [28]. We also we found some cases with a need for dose-adjustments. Most were related to renal insufficiency and some also to cirrhosis and high age, but there was no single drug frequently prescribed with an unadjusted dose. Overall, a total of 22 medication changes following our combined 44 recommendations relating to interactions or dosing in 100 patients suggest that pharmacotherapy could be improved in a considerable proportion and absolute number of hospitalized patients. And although our analysis was not designed and powered to demonstrate a reduction in clinical outcomes and costs, the detection of possible ADE in 4% of the population is in accordance with earlier reports [1-4]. Although relatively rare, an extrapolation to the whole patient population of a hospital would yield a considerable absolute number of preventable ADE and therefore supports the view that local efforts to introduce preventive countermeasures should be increased.

Considering CDSS as such potentially appropriate countermeasures, the results of our study provide important insight into several areas of interest, i.e. the comparative performance, the applicability, and the clinical relevance and potential benefits of CDSS use in routine clinical practice. In contrast to the primarily intended use of CDSS by prescribers and office pharmacists, a key feature of our study is that we as clinical pharmacologists used CDSS as a screening tool for medication errors, whereas the prescribing physicians were not directly confronted with CDSS-generated alerts. Instead, we made a preselection of presumably

clinically relevant alerts where we also used patient-specific information and our clinical expertise, and subsequently also enhanced the automated alerts by additional management recommendations. The rationale for this approach is our own experience as well as an increasing number of reports in the literature [22, 29-34] that identified overalerting as a major issue with currently available CDSS. Indeed, although most alerts could be considered as generally valid, for all three CDSS that we used more than 90% of alerts appeared clinically irrelevant when they were applied to the management of specific patients. Therefore, also in our setting forwarding all alerts without selection would have most likely led to indiscriminate overriding. Furthermore, our finding that many clinically relevant interactions were classified as moderate or even mild according to the classic “traffic light” grading used by all three CDSS indicates that even filtering only “severe” alerts would not be a reasonable solution. Indeed, a previous study also reported that customization of CDSS by common severity levels was not able to improve effectiveness [32]. The more management-oriented Operational Classification of Drug Interactions (ORCA) has been developed with this issue in mind [35], and recently we proposed an extension of ORCA that also supports the implementation of patient-specific information and potential outcomes of drug interactions in CDSS algorithms [28, 36, 37]. Currently ongoing studies that evaluate CDSS based on such management-oriented classifications will show whether they can make a relevant contribution to the reduction of overalerting.

Comparing the three CDSS for their sensitivity to detect clinically relevant interactions, DrugReax and TheraOpt performed better than Pharmavista. This result must certainly be interpreted in consideration of Pharmavista’s inability to analyze more than eight drugs concomitantly, which applied to 42% of our medical inpatient population, and it may be less of an issue in a pharmacy setting, where Pharmavista is frequently used. Nevertheless, our results indicate that it is quite a relevant limitation for a medical inpatient population.

Among all interaction alerts that we considered as relevant 58% were actually followed by according prescription changes. This demonstrates that our preselection based on patient-specific clinical information and adding of management recommendations in combination

with personal communication of the alerts were generally well-received and able to overcome the major problem of overriding of alerts to a large part. For the remaining 42% of alerts that were not followed by a prescription change, clinicians may have either judged our recommendations as not justified (which may or may not be true), or indiscriminative overriding may have occurred. Previous studies named the most frequent reasons for alert overriding: the problem was already known but clinically not important, there were no reasonable alternatives while the benefit was considered to be greater than the risk, the potential problem could be managed by appropriate monitoring, the dose had been adjusted, or the patient had previously tolerated the medication [31, 32]. Similar reasons were brought forward when we contacted the prescribers. Furthermore, we realize some inevitable limitations of our assessments, i.e. in the absence of a gold standard for the clinical relevance of potential medication errors it is possible that we excluded some relevant alerts, oversaw additional medication errors, or on the other hand forwarded some irrelevant alerts. However, neither did we identify additional ADE, nor does it appear likely that the combined sensitivity of the three CDSS plus our manual review failed to identify a relevant number of medication errors.

Regardless of the reason for overriding and the differences that we found between CDSS, the fact that less than 10% of automated alerts were assessed as relevant for individual patients forces us to rethink how future CDSS can be effective and efficient for the prevention of medications errors, ADE and unnecessary costs in clinical practice. Maximum sensitivity may be a common priority in the development of CDSS, and much of their content can be tracked down to the safety information in the manufacturer's prescribing information, where, also for legal reasons, comprehensiveness rather than clinical relevance is determinative. The comprehensive and generally valid alerts and comments from all three CDSS were certainly useful for screening and learning purposes in our setting. However, eventually CDSS must be integrated with CPOE and automatically display alerts that have a high propensity of clinical relevance. Indeed, approaches that target specific relevant problems of pharmacotherapy have demonstrated their efficacy not only to change

prescribing behavior but also to improve clinical outcomes [38]. Therefore, we propose that on the one hand the valuable comprehensive knowledge from CDSS should be easily available (via “one click”) to the prescriber, but only on an on-demand basis. On the other hand, there should be a list with a limited number of automatically computer-triggered alerts. Clinical pharmacologists can initially develop such a list and make a preselection that focuses on clinical relevance and management implications. Also local retrospective systematic evaluations of medication errors and adverse drug events that occurred in the past can contribute to and help to justify the use of such a list [36, 37]. But the list should also be reviewed and supported by local leading clinicians in order to enhance its local acceptance. Furthermore, the importance of patient-specific factors suggests that alert algorithms must also include as much laboratory and clinical information as possible. Indeed, obtaining laboratory results as part of intensified monitoring could also be part of clinical actions recommended and surveyed by CDSS. This requires interfaces that integrate CDSS with laboratory and clinical information systems. For example, alert algorithms may include current electrolyte results and QTc times from automated ECG readings. Although we did not use CDSS with integration into CPOE and clinical information systems in our setting, it is important to note that TheraOpt and other currently available CDSS have indeed been designed in such a way. However, if this approach is used for all interactions of a highly sensitive CDSS, its complexity and applicability will likely become uncontrollable and result once more in overriding.

CONCLUSIONS

The studied CDSS are valuable screening tools for medication errors, but only a small fraction of all alerts are clinically relevant in individual patients. Insufficient use of patient-specific information in alert algorithms and lack of local customization compromise their applicability and efficacy in clinical practice. In addition, lack of scientific evidence in complex individual patient care and common off-label use remain major challenges for CDSS. We

therefore propose that CDSS should separate comprehensive on-demand information from selected computer-triggered alerts that must be locally supported, customized and frequently updated, and have management implications in the majority of patients where they are displayed. The initial setup plus necessary ongoing evaluations and adjustments of such a system requires expertise and additional resources. However, compared to a standard CDSS without appropriate local promotion and support, such an approach may not only be more efficacious but also more efficient.

REFERENCES

1 Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R, et al. (1995) Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 274 (1): 29-34

2 Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP (1997) Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 277 (4): 301-306

3 Lagnaoui R, Moore N, Fach J, Longy-Boursier M, Begaud B (2000) Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. European Journal of Clinical Pharmacology 56 (2): 181-186

4 Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279 (15): 1200-1205

5 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329 (7456): 15-19

6 Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA (2003) Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 289 (13): 1652-1658

7 Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA (2004) Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. The New England Journal of Medicine 351 (6): 543-551

8 Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U (2008) The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. J Am Med Inform Assoc 15 (5): 585-600

9 Feldstein AC, Smith DH, Perrin N, Yang X, Rix M, Raebel MA, Magid DJ, Simon SR, Soumerai SB (2006) Improved therapeutic monitoring with several interventions: a randomized trial. Archives of Internal Medicine 166 (17): 1848-1854

10 Kaushal R, Kern LM, Barron Y, Quaresimo J, Abramson EL (2010) Electronic prescribing improves medication safety in community-based office practices. Journal of General Internal Medicine 25 (6): 530-536.

11 Kaushal R, Shojania KG, Bates DW (2003) Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Archives of Internal Medicine 163 (12): 1409-1416

12 Smith DH, Perrin N, Feldstein A, Yang X, Kuang D, Simon SR, Sittig DF, Platt R, Soumerai SB (2006) The impact of prescribing safety alerts for elderly persons in an electronic medical record: an interrupted time series evaluation. Archives of Internal Medicine 166 (10): 1098-1104

13 Eslami S, de Keizer NF, Abu-Hanna A (2008) The impact of computerized physician medication order entry in hospitalized patients--a systematic review. International Journal of Medical Informatics 77 (6): 365-376

14 van Doormaal JE, van den Bemt PM, Zaal RJ, Egberts AC, Lenderink BW, Kosterink JG, Haaijer-Ruskamp FM, Mol PG (2009) The influence that electronic prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study. J Am Med Inform Assoc 16 (6): 816-825

15 Wolfstadt JI, Gurwitz JH, Field TS, Lee M, Kalkar S, Wu W, Rochon PA (2008) The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. Journal of general internal medicine 23 (4): 451-458

16 Olvey EL, Clauschee S, Malone DC (2010) Comparison of critical drug-drug interaction listings: the Department of Veterans Affairs medical system and standard reference compendia. Clinical Pharmacology and Therapeutics 87 (1): 48-51

17 Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, Lipton RB (2004) Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc 44 (2): 136-141

18 Vonbach P, Dubied A, Krahenbuhl S, Beer JH (2008) Evaluation of frequently used drug interaction screening programs. Pharm World Sci 30 (4): 367-374

19 van Doormaal JE, Mol PG, van den Bemt PM, Zaal RJ, Egberts AC, Kosterink JG, Haaijer-Ruskamp FM (2008) Reliability of the assessment of preventable adverse drug events in daily clinical practice. Pharmacoepidemiology and Drug Safety 17 (7): 645-654

20 Smithburger PL, Kane-Gill SL, Benedict NJ, Falcione BA, Seybert AL (2010) Grading the severity of drug-drug interactions in the intensive care unit: a comparison between clinician assessment and proprietary database severity rankings. Ann Pharmacother 44 (11): 1718-1724

21 Vonbach P, Dubied A, Beer JH, Krahenbuhl S (2007) Recognition and management of potential drug-drug interactions in patients on internal medicine wards. European Journal of Clinical Pharmacology 63 (11): 1075-1083

22 van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A (2009) Drug safety alert generation and overriding in a large Dutch university medical centre. Pharmacoepidemiology and Drug Safety 18 (10): 941-947

23 Thomson Reuters DRUG-REAX SYSTEM. http://thomsonreuters.com/products_services/healthcare/healthcare_products/a-z/drug_reax_system

24 Pharmavista Interactions (2011). http://www.pharmavista.ch

25 ID Berlin ID PHARMA CHECK. http://www.id-berlin.de

26 Albengres E, Le Louet H, Tillement JP (1998) Systemic antifungal agents. Drug interactions of clinical significance. Drug Saf 18 (2): 83-97

27 Hempfling W, Grunhage F, Dilger K, Reichel C, Beuers U, Sauerbruch T (2003) Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. Hepatology 38 (1): 196-202

28 Haueis P, Greil W, Huber M, Grohmann R, Kullak-Ublick GA, Russmann S (2011) Evaluation of drug interactions in a large sample of psychiatric inpatients: a data interface for mass analysis with clinical decision support software. Clinical Pharmacology and Therapeutics 90 (4): 588-596

29 Taylor LK, Tamblyn R (2004) Reasons for physician non-adherence to electronic drug alerts. Stud Health Technol Inform 107 (Pt 2): 1101-1105

30 Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS (2003) Physicians' decisions to override computerized drug alerts in primary care. Archives of internal medicine 163 (21): 2625-2631

31 Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, Recklet EG, Bates DW, Gandhi TK (2006) Improving acceptance of computerized prescribing alerts in ambulatory care. J Am Med Inform Assoc 13 (1): 5-11

32 Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R, Jacques A, Dawes M, Abrahamowicz M, Perreault R, Winslade N, Poissant L, Pinsonneault A (2008) A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. J Am Med Inform Assoc 15 (4): 430-438

33 Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, Weingart SN (2009) Overrides of medication alerts in ambulatory care. Archives of Internal Medicine 169 (3): 305-311

34 Weingart SN, Simchowitz B, Shiman L, Brouillard D, Cyrulik A, Davis RB, Isaac T, Massagli M, Morway L, Sands DZ, Spencer J, Weissman JS (2009) Clinicians' assessments of electronic medication safety alerts in ambulatory care. Archives of

Internal Medicine 169 (17): 1627-1632

35 Hansten PD, Horn JR, Hazlet TK (2001) ORCA: OpeRational ClassificAtion of drug interactions. J Am Pharm Assoc (Wash) 41 (2): 161-165

36 Frolich T, Zorina O, Fontana AO, Kullak-Ublick GA, Vollenweider A, Russmann S (2011) Evaluation of medication safety in the discharge medication of 509 surgical inpatients using electronic prescription support software and an extended operational interaction classification. European Journal of Clinical Pharmacology, Epub ahead of print Jun 14

37 Guzek M, Zorina OI, Semmler A, Gonzenbach RR, Huber M, Kullak-Ublick GA, Weller M, Russmann S (2011) Evaluation of drug interactions and dosing in 484 neurological inpatients using clinical decision support software and an extended operational interaction classification system (Zurich Interaction System). Pharmacoepidemiology and Drug Safety 20 (9): 930-938

38 Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, Goldhaber SZ (2005) Electronic alerts to prevent venous thromboembolism among hospitalized patients. The New England Journal of Medicine 352 (10): 969-977

Acknowledgments

The physicians at the Department of Internal Medicine at the University Hospital Zurich are respectfully acknowledged for devoting time and effort to discuss and improve the patients' pharmacotherapy.

Financial support and conflict of interest statement

The work presented in this manuscript was done independently by the authors and with general resources available at the Department of Clinical Pharmacology. IC, ME and GKU are involved in the development of prescribing software, but there are no relations to the CDSS studied here. All authors declare that they have no conflict of interest regarding this work.

FIGURE LEGENDS AND TABLES

FIGURE LEGENDS

Figure 1 - Procedures

Overview of the pharmacotherapy evaluation process.

Figure 2 - Polypharmacy

Histogram of the polypharmacy distribution for 100 patients.

Figure 3 - Polypharmacy and identification of drug interactions by CDSS

Mean number of identified interactions per patient for each CDSS over polypharmacy categories in 100 patients. Pharmavista did not allow analysis of more than 8 concomitant drugs.

TABLES

Table 1 - Patient characteristics

Characteristics	n
Total	**100**
Sex	
Female	42
Male	58
Age category (years)	
<50	20
50-59	32
60-69	19
70-79	17
≥80	12
Time of pharmacotherapy evaluation (days after admission)	
0-1	16
2-4	33
5-9	37
≥10	14
Disease categories[1]	
Gastroenterology and Hepatology	25
Nephrology	24
Internal medicine	17
Cardiology	11
Angiology	6
Oncology	4
Pneumology	4
Endocrinology	3
Hematology	3
Infectiology	2
Immunology	1
Renal function (GFR, ml/min/1.73m^2)[2]	
≥60	56
30-59	22
<30, no dialysis	11
Dialysis	11
Liver disease with CHILD score ≥7	
Yes	11
No	89
Malignancy	
Yes	25
No	75
Transplantation	
Liver	2
Lung	5
Kidney	16

[1] Only one primary diagnosis per patient

[2] Most recent glomerular filtration rate (GFR) before pharmacotherapy evaluation according to the MDRD-formula

Table 2 - Prescription frequencies for different drug categories

Number of prescriptions and number of patients with such prescriptions for different drug categories

Drug classes	Number of prescriptions		Number of patients with prescriptions
	n	%	n (=%)
Total	**892**	**100**	**100**
Antibiotics	110	12.3	50
Heparins	63	7.1	63
Proton pump inhibitors	60	6.7	60
Diuretics	52	5.8	40
Beta blockers	43	4.8	43
Immunosuppressants	40	4.5	23
HMG-CoA inhibitors	38	4.3	38
Antiplatelets	37	4.2	28
Corticosteroids systemic	34	3.8	34
ACE inhibitors	28	3.1	28
Vitamins	28	3.1	28
Antivirals	26	2.9	15
Calcium salts	22	2.5	22
Laxatives	22	2.5	18
Hormones	20	2.2	17
Calcium channel blockers	19	2.1	19
Antifungals	16	1.8	12
Potassium salts	16	1.8	16
Angiotensin renin blockers	14	1.6	14
Benzodiazepines and GABA agonists	14	1.6	13
Oral anticoagulants	14	1.6	14
Insulins	13	1.5	9
Analgetics metamizole	11	1.2	11
Analgetics opioids	10	1.1	10
Analgetics paracetamol	9	1.0	9
Antidepressants	9	1.0	7
Antiemetics	9	1.0	8
Antiepileptics	9	1.0	7
Oral glucose lowering agents	9	1.0	7
Antiarrhythmics	8	0.9	7
Antiasthmatics	7	0.8	3
Magnesium salts	7	0.8	7
Neuroleptics	7	0.8	7
Antiparkinson drugs	4	0.5	2
Uricostatics	4	0.5	4
NSAIDs	2	0.2	2
Other	58	6.5	44

Table 3 - Identification and evaluation of drug interactions

Identification of drug interactions by CDSS, further expert evaluation, according prescription changes and associated adverse events. First overall results are presented, followed by stratifications over severity grading of interactions.

Identification and evaluation of interactions	PharmaVista[1]		DrugReax		TheraOpt	
	n	%	n	%	n	%
All interactions	**53**	**100**	**362**	**100**	**328**	**100**
Evaluated as clinically relevant (PPV[2])	3	5.7	29	8.0	25	7.6
Sensitivity[3]		9.1		87.9		75.8
Alert followed by prescription change	3	5.7	17	4.7	13	4.0
Adverse event associated with interaction	0	0	3	0.8	3	0.9
Mild interactions	**36**	**100**	**23**	**100**	**213**	**100**
Evaluated as clinically relevant (PPV[2])	3	8.3	0	0	4	1.9
Sensitivity[3]		9.1		0		12.1
Alert followed by prescription change	3	8.3	-	-	4	1.9
Adverse event associated with interaction	0	0	-	-	0	0
Moderate interactions	**17**	**100**	**248**	**100**	**104**	**100**
Evaluated as clinically relevant (PPV[2])	0	0	12	4.8	15	14.4
Sensitivity[3]		0		36.4		42.4
Alert followed by prescription change	-	-	5	2.0	5	4.8
Adverse event associated with interaction	-	-	3	1.2	3	2.9
Severe interactions	**0**	**-**	**91**	**100**	**11**	**100**
Evaluated as clinically relevant (PPV[2])	-	-	17	18.7	6	54.5
Sensitivity[3]		0		51.5		18.2
Alert followed by prescription change	-	-	12	13.2	4	36.4
Adverse event associated with interaction	-	-	0	0	0	0

[1]Pharmavista did not analyze pharmacotherapy if n concomitant drugs was >8

[2]Percentage value equals positive predictive value (PPV): PPV = n interactions identified by the respective CDSS *and* evaluated as clinically relevant / n interactions identified by the respective CDSS * 100.

[3]Sensitivity (%) = n interactions among all 33 interactions evaluated as clinically relevant identified by the respective CDSS / all 33 interactions identified by any source and evaluated as clinically relevant * 100

Table 4: Listing of all drug interactions that were identified by CDSS and evaluated as clinically relevant during expert discussion (29 distinct interactions occurring in 33 instances)

Interacting drugs	CDSS detection and severity grading[1]			Potential adverse event	Mech-anism[2]	Rx change
	PhVis	DRx	ThOpt			
Amiodarone - simvastatin	x	3	2	Myopathy	PK	No
Amiodarone - atorvastatin	x	2	2	Myopathy	PK	Yes
Amiodarone - metronidazole	x	3	x	QT-prolongation	PD	Yes
Amiodarone - cotrimoxazole	x	3	3	QT-prolongation	PD	Yes
Amiodarone - itraconazole	x	3	x	QT-prolongation	PD	Yes
Amiodarone - clarithromycin (n=2)	x	3	3	QT-prolongation	PD	2xYes
Amiodarone - ciprofloxacin	x	3	x	QT-prolongation	PD	Yes
Cyclosporine - simvastatin	x	3	2	Myopathy	PK	Yes
Cyclosporine - pravastatin	x	2	2	Myopathy	PK	No
Cyclosporine - morphine - loperamide	x	x	x	Increased levels of cyclosporine and morphine	PK	No
Tacrolimus - itraconazole	x	3	2	Increased levels of tacrolimus	PK	No
Tacrolimus - clarithromycin	x	2	2	Increased levels of both drugs	PK	No
Tacrolimus - metronidazol	x	2	x	Increased levels of tacrolimus	PK	No
Clarithromycin - domperidone - itraconazol	x	x	2	QT-prolongation	PK	Yes
Clarithromycin - cotrimoxazole (n=3)	x	3	3	QT-prolongation	PD	1x Yes, 2x No
Cotrimoxazole - fluconazole	x	3	x	QT-prolongation	PD	1
Ciprofloxacin - atorvastatin	x	2	2	Myopathy	PK	No
Ciprofloxacin - calcium[3] (n=2)	x	2	2	Decreased efficacy (BV[4] ↓)	PK	Yes / No
Itraconazole - ranitidine	x	2	2	Decreased efficacy (BV[4] ↓)	PK	No
Itraconazole - omeprazole	x	2	2	Decreased efficacy (BV[4] ↓)	PK	No
Itraconazole - pantoprazole[3]	x	2	2	Decreased efficacy (BV[4] ↓)	PK	No
Pipamperone - trimipramine	x	3	2	QT-prolongation	PD	No
Ursodeoxycholic acid - colestyramin	1	x	1	Decreased efficacy (BV[4] ↓)	PK	Yes
Daptomycin - pravastatin	x	x	2	Myopathy	PD	Yes
Torasemide - HCTZ - prednisone[3]	x	2	1	Hypokalemia	PD	Yes
Ginkgo biloba - acetylsalicylic acid	1	3	1	Bleeding	PD	Yes
Ginkgo biloba - clopidogrel	1	2	1	Bleeding	PD	Yes
Clopidogrel - esomeprazole	x	3	x	Decreased clopidogrel efficacy	PK	Yes
Terlipressin - quetiapine	x	3	x	QT-prolongation	PD	Yes

[1] Key for severity grading: 1 = mild, 2 = moderate, 3 = severe, x = not detected; PhVis = Pharmavista, DRx = DrugReax, ThOpt = Theraopt.

[2] PK = pharmacokinetic, PD = pharmacodynamic.

[3] Associated with adverse event (see text).

[4] BV = bioavailability, refers to the first drug of the listed combination

Table 5: Dosing recommendations initially identified by TheraOpt that we evaluated as clinically relevant.

Actual prescription[1]	Dosing issue	Prescription change
Zolpidem 10 mg	>65 yrs standard dose 5 mg	Yes / No
Chlortalidon	Contraindicated in severe renal impairment	Yes
Budesonid[2]	In cirrhosis high first pass	Yes
Hydrochlorothiazide	Contraindicated in severe renal impairment	No
Metformin	Contraindicated in severe renal impairment	No
Simvastatin 40 mg	Max. 10mg if GFR[3]<30	No
Metamizol 3 g	Lower dose in renal impairment	No
Pantoprazol 40 mg	In cirrhosis max. 20 mg	No
Clarithromycin 2x250 mg	Max. 250 mg if GFR[3]<30	No

[1] n=1 for all dosing errors with the exception of zolpidem 10 mg (n=2)

[2] Associated with adverse event (see text)

[3] GFR = glomerular filtration rate